REMARKS

Claim Status

Claims 1, 14-23, and 25-29 are pending in the application. The Examiner has rejected claims 1, 14-23, and 25-29. Applicant has added new claims 30 - 33. The new claims do not contain new matter.

Claim Rejections - 35 U.S.C. § 112 – First Paragraph

Examiner's should reconsider the rejection under § 112 (first paragraph) because application of the *Wands'* factors favor enablement.

Pursuant to *In Re Wands* and MPEP § 2164.01(a), the following factors are relevant to the issue of enablement: (a) the quantity of experimentation needed to make or use the invention based on the content of the disclosure, (b) the amount of direction provided by the inventor, (c) the existence of working examples, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art (g); the level of predictability in the art, and (f) the breadth of the claims. If a patent application would have taught one skilled in the art how to use the full scope of the claimed invention without undue experimentation, such application has been enabled. *See, In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

1. **Examiner's rejection under § 112 (first paragraph) is improper because no experimentation is needed to make or use the invention based on the content of the disclosure.**

"A patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01, citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991);

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

In this case, the patent application enables a person who regularly treated patients with retroviruses to use the invention claimed. *See generally,* declarations of David Sidebottom, MD, ("Sideb'm Decl.") and Michael F. Murray, MD ("Mur. Decl."). For one thing, even though the specification need not disclose what is well known to those skilled in the art, the application provides information on the administration of niacin and well as cites references for the reader to learn more information about the administration and effects of niacin. *See generally,* application; *see also,* Sideb'm Decl., ¶ 8(a); Mur. Decl., ¶ 27(a). In addition, medical doctors or those in the medical field are often familiar with niacin. Sideb'm Decl., ¶ 8(b); Mur. Decl., ¶ 27(a). Those who are not readily familiar with niacin know that much information can be found regarding the administration and effects of niacin on "Medline", in journals, books and other commonly available resources. *Id.*

The application tells a reader that the preferred method to combat plasma tryptophan depletion is to "administer niacin in `pharmacological doses'". Sideb'm Decl., ¶ 8(c); Mur. Decl., ¶ 27(b); *see also* application, pg. 7, line 12. The application recommends that a reader administer a dose greater than 20 milligrams per day because a lesser dose would not be expected to produce the pharmacological effect of combating plasma tryptophan depletion. Sideb'm Decl., ¶ 8(d); Mur. Decl., ¶ 27(c); *see also* application, pg 8, line 1.

The application informs a reader that the preferred dose is 500 milligrams of niacin per day. Sideb'm Decl., ¶ 8(h); Mur. Decl., ¶ 27(g); *see also* application, pg. 9, lines 3-4. The

application informs a reader to expect pharmacological activity to begin occurring at a dose of 100 milligrams per day. Sideb'm Decl., ¶ 8(e); Mur. Decl., ¶ 27(d); *see also* application, pg. 8, lines 10-11. The application informs a reader to expect a patient to undergo a reverse systemic tryptophan depletion upon the daily administration of 100 milligrams of niacin. Sideb'm Decl., ¶ 8(f); Mur. Decl., ¶ 27(e); *see also* application, pg. 8, lines 10-15. The application informs a reader that the preferred method of administration of niacin in this invention is oral administration. Sideb'm Decl., ¶ 8(g); Mur. Decl., ¶ 27(f); *see also* application, pg 9, lines 2-3. The application informs a reader that the preferred form of niacin to practice this invention is nicotinamide. Sideb'm Decl., ¶ 8(i); Mur. Decl., ¶ 27(h); *see also* application, pg. 9, lines 3-4.

By way of example, the application informs a reader that administering 3 grams of nicotinamide per day for two months can be expected to increase plasma tryptophan between 20% and 80%. Sideb'm Decl., ¶ 8(j); Mur. Decl., ¶ 27(i); see also application, Table 3. It is known that a safe maximum dose for nicotinamide is 3 grams per day and this readily supported by the medical literature. Mur. Decl., ¶ 27(j); M. Knip et al., Safety of High-Dose Nicotinamide: A Review, 43 Diabetologia 1337-1345 (2000), a copy of which is attached to the Mur. Decl. as Exhibit E.

The laboratory parameter to monitor plasma tryptophan concentrations is widely available. Mur. Decl., ¶ 27(k). The application provides expected baseline systemic tryptophan levels and expected increases in systemic tryptophan. Mur. Decl., ¶ 27(l); *see also* application, Table 3. Furthermore, medical literature provides gives expected and target tryptophan levels. Mur. Decl., ¶ 27(l). For example, Werner et al came up with 91 micromol/l as a baseline for systemic tryptophan from their study on tryptophan and HIV in 1988. *See* **Exhibit B** to Mur. Decl.. Other studies have come up with different normal tryptophan levels - generally lower

than 91 - but Werner and collegues have stated their normal as 91 in three different studies. *See id.* Medical literature also establishes goal levels for tryptophan [by comparing tryptophan values in patients with HIV infection to healthy control patients] make this an easily administered pharmacological agent. *Id.*

For all of the foregoing reasons, no undue experimentation is necessary before someone in the medical field could practice this invention.

2. Examiner's rejection under § 112 (first paragraph) is improper because the specification contains within it a connotation of how to use the invention.

"35 U.S.C. 112 is satisfied if a statement of utility in the specification contains within it a connotation of how to use the invention...." MPEP § 2164.01(c). "For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph." *Id; see, e.g., Application of Johnson*, 282 F.2d 370 (P.App. Cir. 1960).

In this case, it is typical that patients with retroviral infections will periodically ask their physician to administer a "non-prescription" therapy, and physicians will then work with patients in an attempt to safely achieve the trial of therapy requested. Mur. Decl., ¶ 26(a). In fact, in a recent study by Hsiao et al. over half of the retrovirally infected patients in the study were taking non-prescription therapies, and two-thirds of those patients discussed these therapies with their physicians. *See id.*

In addition, those in the medical field recognize that no two patients are the same.

Sideb'm Decl., ¶ 9; Mur. Decl., ¶ 28. Those in the medical field also recognize that different patients react differently to the same treatment. *Id.* Patients react differently to the same treatment for a myriad of reasons including different diets, different stress levels, different genetic makeup, and different metabolic rates. *Id.* These observations make the determination of optimal dosing of a drug in a particular case an individualized process. *Id.* Against this backdrop, the specification enables one in the medical field to practice the invention without undue experimentation. *See* Sideb'm Decl., ¶ 11-13; Mur. Decl., ¶ 30(a).

Based on the information contained in the application, a doctor would likely, in the ordinary case. confirm both retroviral infection and tryptophan depletion with simple blood tests, and then initiate treatment for tryptophan depletion by orally administering a daily dose of nicotinamide in the preferred amount of 500 milligrams per day. Sideb'm Decl., ¶ 10(a); Mur. Decl., ¶ 29(a). In a more extreme case of tryptophan depletion, a doctor would likely initiate treatment by orally administering a daily dose of nicotinamide in the preferred amount of 3 grams per day. Sideb'm Decl., ¶ 10(b); Mur. Decl., ¶ 29(b). In either case, a doctor would probably re-assess the patient at a subsequent date. Sideb'm Decl., ¶ 10(c); Mur. Decl., ¶ 29(c). If the tryptophan levels had increased a doctor would maintain the treatment until tryptophan level had returned to an appropriate level. Sideb'm Decl., ¶ 10(c); Mur. Decl., ¶ 29(c). If the tryptophan level had not increased, a doctor would raise the dosage commensurate with the condition. Sideb'm Decl., ¶ 10(c); Mur. Decl., ¶ 29(c).

Thus, no undue experimentation is necessary for someone in the medical field to practice this invention.

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3. Examiner's rejection under § 112 (first paragraph) is improper because the direction provided by the inventor enables one skilled in the art to practice the invention.

"[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." MPEP § 2164.06 citing *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " MPEP § 2164.06, quoting *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

For example, in *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. *Id.; see also* MPEP § 2164.06. The *Techtronics* court ruled that since one embodiment and the method to determine dose/response was set forth in the specification, the specification was enabling. *Id.* The question of time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation." MPEP § 2164.06.

In this case, Applicant has provided evidence that no experimentation is necessary to practice the invention. *See generally,* Sidebottom and Murray declarations and argument provided in sections 1 and 2, *supra,* pages 6-10.

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4. Examiner's rejection under § 112 (first paragraph) requiring "exhausitive examples" that "define a class of compounds" is improper given the nature of the invention.

The Federal Circuit has expressly rejected the notion that controlled testing in a limited number of humans is insufficient.

The MPEP notes that examiners should give "special consideration" to asserted therapeutic or pharmacological utilities. *See* MPEP § 2107.03. While Examiner's rejection is nominally based on non-enablement under §112 not lack of utility under §101, Examiner's §112 rejection effectively and improperly requires Applicant to have completed Phase II testing. Effectively requiring Application to have completed Phase II testing is improper.

In an opinion quite critical of a §112 (first paragraph) rejection, the Federal Circuit warned against rejecting a claim under §112 because testing had only been performed on a limited number of individuals and limited dosage regimes. *See, e.g., In Re Brana*, 51 F.2d 1560 ¶ 35 (Fed. Cir. 1995). In *Brana*, the Court described the difference between Phase I and Phase II testing. Phase I testing is typically based on limited human studies or animal studies. Phase II testing, on the other hand, is more extensive and often used to "determine primarily...[a drug's] potential efficacy under different dosage regimes" and to apply the dosage regimes to a large sample of humans. *Id.*

As it had on several occasions before, the Court denounced the notion that a patent applicant needed to provide a level of detail that could only be achieved through Phase II testing. Indeed, the Court expressly stated "[w]ere we to require phase II testing in order to prove utility, the associated costs would prevent many companies form obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." *Id.* at ¶ 36.

As a result, the court concluded that the applicant's disclosure complied with 35 U.S.C. § 112.

Here, Applicant has not conducted Phase II testing. However, Examiner's basis of rejection under §112 effectively requires applicant to have completed Phase II testing. This is not a proper requirement. Applicant disclosed all of its Phase I testing in its application. The Phase I testing showed a statistically significant change in systemic tryptophan based on administration of niacin compounds in patients with normal dietary intakes of niacin and tryptophan. No one had ever discovered this use for niacin before.

Examiner's rejection that Applicant has "failed to provide sufficient working examples" cannot be reconciled with *In Re Brana.* In order for Applicant to have provided more examples in his specification, Applicant would have had to have conducted Phase II testing. Thus, for Examiner to criticize Applicant for not providing more examples is improper. Similarly, Examiner's rejection that "these examples are not exhaustive, nor define a class of compounds" is equally improper. As noted by the *Brana* court, Phase II testing is used to "determine primarily...[a drug's] potential efficacy under different dosage regimes" and to apply the dosage regimes to a large sample of humans. *Id.* For the Examiner to require "exhaustive examples" that "define a class of compounds" improperly requires Applicant to have completed Phase II testing.

5. Examiner's rejection under § 112, First Paragraph is improper because the state of the prior art favors enablement.

"The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains." MPEP § 2164.05(a) "The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to

meet the enablement requirement." MPEP § 2164.05(a). "The state of the prior art is also related to the need for working examples in the specification." MPEP § 2164.05(a). "In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used." MPEP § 2164.05(a).

In this case, the state of the prior art with respect to the administration of niacin was well developed at the time the application was filed. *See generally,* Sidebottom and Murray declarations and argument provided in sections 1 and 2, *supra,* pages 6-10. Those in the art knew the various ways to administer niacin as well as the upper limits of safe doses. Mur. Decl., ¶ 27. What was unknown in the art was that the administration of niacin alleviates systemic tryptophan. *Id.,* ¶ 6-20. The application provided this previously unknown aspect. *Id.* Thus, the combination of what was known in the art and what was provided by the application has enabled those in the art to practice the invention. *See generally,* Sidebottom and Murray declarations and argument provided in sections 1 and 2, *supra,* pages 6-10.

6. Examiner's rejection based on § 112 (first paragraph) is overbroad because the working examples of the specification preclude a finding of non-enablement--at least for the examples shown.

"A single working example in the specification for a claimed invention is enough **to preclude a rejection** which states that nothing is enabled since at least that embodiment is enabled." MPEP § 2164.02. Here, Examiner objects to the specification and has rejected **all claims** as "failing to adequately teach how to make and/or use the invention, and thereby failing to provide an enabling disclosure." (Paper 12 at 2.) The MPEP, however, expressly precludes such a rejection when at least one example is provided in the specification. MPEP § 2164.02.

In this case, Applicant has provided four working examples. (See Specification, including Tables 1-4. As expressly set forth in the specification:

> Four HIV infected persons participated in a trial of niacin in the form of nicotinamide. The participants were at various stages of their HIV infection as judged by their CD4 counts which ranged from 0 to 620 [see table 1]. The participants were receiving either a stable regimen of anti-viral drugs [i.e. anti-HIV drugs] for a period greater than one year or were not taking any anti-viral drugs. Two of the participants had known co-infections infections typical of HIV infected persons. Each participant took 3 grams of nicotinamide per day for 2 months. This treatment was not associated with any adverse side effects. Each participant's plasma tryptophan was measured prior to treatment and at the end of treatment [see table 3]. The average increase of plasma tryptophan of all participants was 43.9%. This change in tryptophan concentration was statistically significant with a calculated p value of p=0.0112 [using paired t-test]. The study also measured 4 other plasma amino acids which are listed in table 4. All amino acid concentrations were measured by High Performance Liquid Chromotography [HPLC]. There was no significant change in the plasma amino acid concentrations other than tryptophan. As demonstrated in tables 3 and 4, only plasma tryptophan changed in a statistically significant manner.

(emphasis supplied). Thus, at a minimum, claims directed to administering 3 grams of niacin per day to increase plasma tryptophan levels have been enabled by the examples presented in the specification.

7. Examiner's rejection based on § 112 (first paragraph) is improper because Examiner has failed to state why one would not expect to be able to extrapolate the four examples over the entire scope of the claims.

"To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." MPEP § 2164.02. Here, Examiner baldly asserts that the "pharmaceutical art is unpredictable" but does not explain why one would not expect to be able to extrapolate the four examples over the entire scope of the claims. Applicant offers controverting evidence that one skilled in the art would expect to be able to extrapolate the examples provided in the specification across the entire scope of the claims. Sideb'm Decl., ¶ 14; Mur. Decl., ¶ 33-34.

The application provides statistically significant human clinical data with respect to the administration of 3 gms/day of niacin. *See* application, Table 3. It is known in the art that a

normal dietary intake of niacin by one infected with a retrovirus can still leads to systemic tryptophan depletion in some cases. *See* Mur. Decl, ¶ 20; Exhibit B to Mur. Decl.. One knowledgeable in the field of infectious diseases could reasonably extrapolate the findings at 3 gms/day to a range in excess of a normal dietary intake of niacin. Sideb'm Decl., ¶ 14; Mur. Decl., ¶ 33-34. Given that the recommended daily dose of niacin is approximately 20 milligrams per day, one would expect a favorable systemic tryptophan result between a range of 100 mgs/day and higher. Sideb'm Decl., ¶ 14; Mur. Decl., ¶ 33-34.

8. Examiner's § 112, First Paragraph rejection is improper because the relative skill of those in the art favors enablement.

The art recognizes that standard modes of administration are known and contemplated.

"35 U.S.C. 112 is satisfied if ... the art recognizes that standard modes of administration are known and contemplated." MPEP § 2164.01(c). "If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." *Id.*

Applicant claims a "method of increasing systemic tryptophan comprising the administration of an effective amount of niacin for increasing systemic tryptophan..." An effective amount begins at a "pharmacological dose" of niacin. Prior to June 30, 2000 it was known that a pharmacological dose is a dose "whereby a pharmacodynamic action is evidenced that is distinct from the nutrient function." See e.g., Joseph R. DiPalma and William S. Thayer, Use of Niacin as a Drug, 11 Annu. Rev. Nutr. 169-87, 170 (1991). In this case, a pharmacological dose is the dose at which niacin stops acting as a nutrient and starts acting to

inhibit and/or reverse the retroviral induced metabolic derangement.

As stated on page 8, line 10 of the Applicant's application, "a pharmacological dose of niacin generally occurs at a dose of about 100 milligrams per day...." Reading the "description" section of the application as a whole, the 100 mg/day dose is the lower limit of pharmacologic activity. As shown in by the four examples set forth in the application, 3 g/day is also an effective pharmacologic dose. And, as stated on page 9, line 3, 500 mg/day is the preferred pharmacologic dose. Thus, applicant has defined the lower limit of the metes and bounds of the claimed invention as 100 mg/day.

The upper limit was also known in the art prior to June 30, 2000. The safety of high doses of niacin in the form of nicotinamide and nicotinic acid has been explored by those in the art for more than 50 years. Mur. Decl., ¶ 27(j); *see also*, M. Knip et al., Safety of High-Dose Nicotinamide: A Review, 43 Diabetologia 1337-1345 (2000) which is attached to Murray's Declaration at Exhibit E. It was known prior to June 30, 2000 that doses up to 3 g/day are considered safe and well tolerated. Id. at 1343-44. Higher doses of up to 6 g/day have exhibited some side effects, including nausea. Id. at 1343. And, a case of reversible hepatotoxicity occurred in a patient taking 9 g/day. Id. No other significant side effects were reported.

Applicant has claimed a specific use for niacin in doses that are greater than 100 mg/day and less than the toxic limit, which is believed to be in excess of 9g/day. At a minimum, applicant has enabled a range of pharmacologic doses between 100 mg/day and 9 g/day. Accordingly, Applicant respectfully requests that the examiner reconsider his conclusion that the instant claims "necessitate an exhaustive search for the embodiments suitable to practice the claimed invention" and that the instant claims fail to specify the "metes and bounds" of the patent protection desired.

9. Examiner's rejection based on § 112, First Paragraph is improper because the level of predictability in the art

Applicant has disclosed at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims.

"The enablement requirement if 35 U.S.C. § 112 is satisfied as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim." MPEP § 2164.01(b). As previously noted, Applicant has provided four working examples. *See,* Section 6, *supra,* pages 14 and 15. Thus, at a minimum, claims directed to administering 3 grams of niacin per day to increase plasma tryptophan levels have been enabled by the examples presented in the specification.

Furthermore, Pages 7 and 8 of the application describe what the term "pharmacological dose" means. The balance of the application sets fort the "metes and bounds." As stated on page 8, line 10 of the Applicant's application, "a pharmacological dose of niacin generally occurs at a dose of about 100 milligrams per day...." Reading the "description" section of the application as a whole, the 100 mg/day dose is the lower limit of pharmacologic activity. As shown in by the four examples set forth in the application, 3 g/day is also an effective pharmacologic dose. And, as stated on page 9, line 3, 500 mg/day is the preferred pharmacologic dose. Thus, applicant has defined the lower limit of the metes and bounds of the claimed invention as 100 mg/day.

Applicant has claimed a specific use for niacin in an "effective amount." As disclosed and enabled in the application an effective amount is one that creates pharmacoligic activity. It is expected that an effective amount would begin to occur at a dose greater than 100 mg/day. At a minimum, applicant has enabled a range of pharmacologic doses between 100 mg/day (the lower limit) and 3 g/day (the dose administered in the four examples). Accordingly, Applicant respectfully requests that the examiner reconsider his conclusion that the instant claims

"necessitate an exhaustive search for the embodiments suitable to practice the claimed invention" and that the instant claims fail to specify the "metes and bounds" of the patent protection desired.

10. Examiner's rejection based on § 112, First Paragraph is improper because the breadth of the claims favor enablement

"Where the invention resides in finding the activity rather than in discovering some critical range or the like, we have approved of such broad definitions of quantity or dosage. *In re Caldwell*, 319 F.2d 254, 50 CCPA 1464 (1963); compare *In re Halleck*, 422 F.2d 911, 57 CCPA (1970); *Application of Gardner*, 427 F.2d 786, 788 (P.App. Cir. 1970)("Claims 4 and 5 call for "daily dosages" in the ranges 10 to 450 mg. and 10 to 300 mg., respectively. They are enormously wide ranges but there is nothing indefinite about them").

In this case, the invention centers on the discovery that the administration of a daily dose of niacin in patients already receiving adequate dietary intakes of both tryptophan and niacin results in increased levels of systemic tryptophan. No one had ever considered this before. *See* Mur. Decl., ¶¶ 6-20. Thus, broad claims to this invention are appropriate.

Claim Rejections - 35 U.S.C. § 112 – Second Paragraph

Examiner's rejection under § 112, First Paragraph is inconsistent with earlier positions taken by Examiner.

The Examiner has rejected all pending claims under 35 U.S.C. § 112, second paragraph, as "indefinite" and "failing to set forth the metes and bounds of the patent protection desired." Further, Examiner claims that an "effective amount" is not set forth in the specification. Applicant has previously demonstrated that the application enabled the metes and bounds of the claims. *See* Response, *supra*.

In light of the Examiner's previous suggestion on page 10 (paper 7) to use a different

word than "pharmacological", Applicant has since substituted the word "effective amount" for the recited "pharmacological" in the relevant claims. The use of the term "effective amount" has been held appropriate in similar cases. *See, In re Caldwell*, 319 F.2d 254, 50 CCPA 1464 (1963) ("Where the invention resides in finding the activity rather than in discovering some critical range or the like, we have approved of such broad definitions of quantity or dosage"); *In re Halleck*, 442 F.2d 911(C.C.P.A. 1970) (approving use of the term "effective amount"); *Application of Gardner*, 427 F.2d 786, 788 (P.App. Cir. 1970)("Claims 4 and 5 call for "daily dosages" in the ranges 10 to 450 mg. and 10 to 300 mg., respectively. They are enormously wide ranges but there is nothing indefinite about them."). Furthermore, the term "effective amount" is expressly used in the specification (page 5, line 4-5 and page 6, line 11) and is unmistakably implied by the specification as a whole. Thus, Examiner should reconsider his rejection.

Claim Rejections - 35 U.S.C. § 103
(claims 1,14-21, 23, 24 and 26-29)

Claim Rejections - 35 U.S.C. § 103
(claims 22 and 25)

The Examiner has rejected claims 1, 14-21,23,24 and 26-29 under 35 U.S.C. § 103 as being unpatentable over Tang et. al, Brown et al, in view of Murray et. al. Applicant respectfully requests Examiner to reconsider and withdraw of the rejections of record with respect to the obviousness rejection under 35 U.S.C. § 103.

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1. Applicant's invention is directed to increasing systemic tryptophan not anti-HIV therapy.

Examiner's states that Tang et al and Brown et al teach that elevated levels of niacin "significantly decreas[es] the progressions of HIV infected individuals to AIDS." (page 5 of paper 12.) Applicant's invention is different. The invention set forth in the application is not directed to antiviral therapy. Mur. Decl., ¶¶ 31-32; *see also* Sideb'm Decl., ¶ 13. The invention set forth in the application is directed to treating patients with systemic tryptophan depletion. *Id.*

Moreover, any study claiming niacin for anti-viral effect may not be relied upon due to potential inoperability. The *in vivo* study set forth in the application did not show that the administration of niacin had any anti-viral effect. Mur. Decl., ¶32. No *in vivo* study has been able to show that niacin in any amount has any anti-viral effect. *Id.*

In this case, Applicant has discovered a method of increasing systemic tryptophan of humans through the administration of niacin. Mur. Decl., ¶6. Applicant's invention is new, useful and non-obvious.

2. A §103 rejection is improper because a positive clinical outcome from high doses of niacin does not necessarily flow from the Examiner cited prior art.

An "inherent characteristic" necessarily flows from the teachings of the prior art." MPEP § 2112, (Section titled *Examiner Must Provide Rationale of Evidence Tending to Show Inherency*)(citing *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(empahsis in original). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency.]" *In Re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993)(quoting *In re Oelrich,* 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). In this case, not all HIV patients have depleted tryptophan levels. Mur. Decl., ¶ 6.

Here, Examiner's claim that Applicant's invention is inherent in light of Tang et al because Tang et al allegedly teaches a positive clinical outcome for HIV infected patients is incorrect. While there is a correlation between retroviral infection and tryptophan depletion there is significant interpatient variability. Mur. Decl., ¶ 6; *see also* Exhibit B to Mur. Decl.. Thus, not every patient infected with a retrovirus will necessarily require the intervention suggested by the invention disclosed in the application. *Id.* The invention disclosed in the application will specifically benefit patients in need of therapy to maintain or increase their systemic tryptophan levels. *Id.* As a result, Examiner's citation to the inherency doctrine is not correct because a positive clinical outcome will not necessarily occur through the practice of this invention on all retrovirally infected patients.

3. Examiner should reconsider the § 103 rejection because obviousness cannot be predicated on a non-enabling disclosure.

Obviousness cannot be predicated on a non-enabling disclosure. MPEP § 2121.01. "A reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention. *Id.* "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 2141.03

In this case, the public was not in possession of the claimed invention. In late 1998 – after Tang, Brown and Murray 1995 – experts noted that niacin use in treating retroviruses had never been shown and was purely speculative. For example, one expert stated:

> many HIV infected people take vitamin supplements and there have never been reports on any major effect on the clinical course except for vitamin A. Many individuals and researchers have ideas that vitamins may provide some clinical benefit in HIV infection by the niacin theory

> needs much better substantiation and of course some kind of clinical trial. Thus at this point the concept is so purely speculative...

See, Mur. Decl., ¶¶ 13-20; *See also,* The Lancet peer review attached as Exhibit D to Mur. Decl..

Another expert agreed. *See*, Mur. Decl., ¶ 18; *See also,* The Lancet peer review attached as Exhibit D to Mur. Decl.. The other expert also noted that while Tang, et al. claimed a positive clinical outcome with niacin, Tang's study may have been due to "confounding factors" and/or the presence of other B vitamins. *Id.*

In addition to experts in the field declaring speculative what Examiner claims is obvious, the Tang study is simply different. Mur. Decl., ¶20. Niacin occurs naturally in the diet as a nutrient, and it is very difficult to obtain a niacin free diet. *Id.* Tang et al's observation that patients with high verses low nutrient amounts of niacin in their diet correlate with different outcomes is distinct from the patent application examples, where the patients were prospectively given a dose of niacin designed specifically to exceed nutrient amounts and to act in a manner which was pharmcodynamically distinct from nutrient amounts of niacin. *Id.* While Tang et al simply observes a correlation between micronutrient intake levels of niacin and then speculates that it may relate to a role for niacin in "immune function" [page 1252], the examples provided in the patent establish the unexpected finding that high doses of niacin given therapeutically to retrovirally infected patients with normal nutrient intakes results in improved tryptophan levels.

RR Brown did not enable the public either. RR Brown taught treating tryptophan depletion with tryptophan – not niacin. Mur. Decl., ¶ 38-40. Thus, in addition, Brown cannot be relied on because he taught away from niacin therapy. In his 1991 paper titled "Implications of Interferon-Induced Tryptophan Catabolism in Cancer, Auto-Immune Diseases and AIDS", Dr. RR Brown discussed the implications of tryptophan metabolism to HIV and AIDS. Dr. RR

Brown recognized the importance of looking for a way to therapeutically intervene with respect to systemic tryptophan depletion. *Id.* At no time in his 1991 paper -- or anywhere else -- did Dr. Brown suggest tryptophan depletion could be treated with niacin. *Id.*

In his 1991 paper, Dr. Brown hypothesized that decreased tryptophan might lead to decreased niacin (something that Skurnick later disproved). Dr. Brown also suggested treating tryptophan deficiency with tryptophan. *Id.* Dr. Brown did not suggest niacin therapy for patients with HIV or other retroviral infections. *Id.* Dr. Brown's failure to suggest niacin cannot be considered a oversight since Dr. Brown is a prominent tryptophan researcher with a body of work encompassing over 100 articles stretching back to the 1950s. *Id.*

Thus, Tang and Brown had not enabled experts in the field to be in possession of niacin therapy for tryptophan depletion as of June 30, 2000. Murray 1995 cannot be relied on either because it is equally non-enabling -- Murray 1995 has already been declared non-enabling by the USPTO.

The USPTO has previously found the information relied on by Murray 1995 as speculative and non-enabling. *See* Mur. Decl., ¶¶ 35-37. In 1995, Murray published two articles, both already made of record: (1) MF Murray, et al., Nicotinamide Inhibits HIV-1 in Both Acute and Chrinic *In Vitro* Infection, Biochemical and Biophysical Research Communications, 210:954-959 (1995) and (2) MF Murray, et al., HIV Infection Decreases Intracellular Nicotinamide Adenine Dinucleotide [NAD], Biochemical and Biophysical Research Communications, 212:126-131 (1995). (Collectively, these articles are referred to as the "1995 articles.")

The 1995 articles were base on *in vitro* data. The same *in vitro* data that formed the basis of the 1995 articles also formed the basis of a patent application filed with the United States

Patent and Trademark Office ("USPTO"), U.S. patent application 07/906,689 (the "'689 application"). A true and correct copy of the '689 application is attached to the Mur. Decl. as **Exhibit F.** The USPTO rejected the '689 patent application as non-enabling and unpatentable because it lacked *in vivo* substantiation, specifically:

> The specifications provide data only for inhibiting HIV in cells in culture. There is no data to substantial the alleged utility for treating human subjects infected with HIV. There is **no data to substantiate the alleged utility for treating human subjects infected with HIV**.... Without statistically significant data documenting the claimed method for treating patients, the person of ordinary skill in the art, knowing the unpredictability of extrapolating from in vitro results to in vivo performance, would have good reason to doubt the efficacy of applicant's invention.

See **Exhibit F**, USPTO office action, page 2-3, rejections under §101 and § 112 (emphasis supplied). A true and correct copy of the August 25, 1992 office action is also attached to the Mur. Decl. as **Exhibit F.**

The infectious disease community has been aware of the possibility of tryptophan depletion occurring in patients with HIV since at least as early as 1988. *See, e.g.,* Exhibit B to Mur. Decl. None of the medical literature suggests that the administration of niacin to restores tryptophan levels. *See* Exhibit B to Mur. Decl. No one of ordinary skill in the art could have combined the Examiner cited prior art (Tang, Brown, Murray 1995) with his [or her] own knowledge to make the claimed invention as required before prior art can be considered enabling. The medical community and the USPTO found the Examiner's prior art (Tang, Brown, and Murray 1995) to be non-enabling. Thus, Tang, Brown, and Murray cannot and should not be relied upon here either as the basis for an obvious rejection.

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4. Examiner should reconsider the § 103 rejection because obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established

Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). In this case, the infectious disease community has been aware of the possibility of tryptophan depletion occurring in patients with HIV since at least as early as 1988. *See, e.g.,* Exhibit B to Mur. Decl. Nowhere has anyone other than Murray 1999, which is not "prior art", suggested the administration of niacin to restore tryptophan levels. Mur. Decl., ¶¶ 7-8.

5. Examiner's view of the inherency doctrine is overbroad.

An "inherent characteristic" necessarily flows from the teachings of the prior art." MPEP § 2112, (Section titled *Examiner Must Provide Rationale of Evidence Tending to Show Inherency*)(citing *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(empahsis in original). Claims directed to the novel application are not obvious unless they necessarily flow from the prior art. *See e.g., In re Halleck* 422 F.2d 911 (C.C.P.A. 1970); *In re Caldwell*, 50 C.C.P.A. 1464, 1468-69, 319 F.2d 254, 257-58 (1963).

In *Halleck*, a case remarkably similar to this case, the applicant sought method claims directed to "animal feed and an effective amount of a peristalsis-regulating substance contained therein for growth stimulation." 422 F.2d at 912. The Merck "reference disclosed use of the parasympatholytic agents for relaxing smooth muscles," in similar amounts as claimed by the applicant. *Id.* at 912. The Examiner denied the claims as inherently obvious because Merck disclosed administration of the same substance in similar amounts as the claim at issue, and was

thus "inherently" disclosed by Merck. *Id.* In addition, the examiner rejected the claims as obvious in light of Goodman in view of a Journal Article and Merck because those references suggested an increased caloric intake when intestinal time is increased. *Id.* In light of these references, the Examiner concluded that it would be "obvious to increase intestinal time in order to improve utilization of the feed and growth." *Id.*

The Court of Customs and Patent Appeals ("CCPA") rejected both of the examiner's arguments because:

> Appellant's invention is not merely a composition comprising an animal feed and a peristalsis-regulating substance nor a method of administering a peristalsis-regulating substance to animals. Rather, what is alleged to be **novel and unobvious is the discovery that a peristalsis-regulating substance will stimulate animal growth.** No prior art suggests this.

Id. (emphasis supplied). The CCPA found that the claims were not obvious because the prior art of record was silent with respect to stimulating animal growth by administration of peristalsis-regulating substances. *Id.* at 914. In this case, the prior art is silent with respect to increasing systemic tryptophan with the use of niacin in patients with normal dietary intakes of niacin and tryptophan. As such, the claims are not inherently obvious.

In *Caldwell*, another case remarkably similar to this case, the applicant sought method claims directed to "supplying an effective amount of aspirin for growth stimulation." *Id.*, 50 C.C.P.A. at 1465, 319 F.2d at 255. The Court of Customs and Patent Appeals ("CCPA") noted that while aspirin had been administered to children and rats and the growth rates measured, the claims were not obvious because nothing in the prior art suggested **the use** claimed by the applicant:

> Although aspirin is practically our national drug, it does not appear from anything on the record that its use as a growth promoter for any animal, human or otherwise, has ever been even suggested. As for the reference, we

> are in complete agreement with the appellant, whose brief states: `It seems pretty clear that the Gross reference stands for, and suggests, only one thing as far as the present case goes. That is, that feeding aspirin to children and rats over prolonged periods does not interfere with or retard growth of these two species of animals. As far as aspirin goes, this is the only teaching that can be derived from the reference.'"

Caldwell, 50 C.C.P.A. at 1466, 319 F.2d at 256. **The CCPA went on to say that the "real novelty" is "stimulating the growth of ruminants, poultry, or swine by feeding them aspirin for that purpose."** *Id.* 50 C.C.P.A. at 1468, 319 F.2d at 257 (emphasis supplied). "We therefore disagree...that the "real novelty" must reside in the amount of aspirin fed, rather than in the feeding of aspirin for the stated purpose." *Id.*

In this case, Examiner claims that Applicants invention is not patentable because it is "inherent" in the prior art." (*See* pages 6-7 of paper 12). Examiner's interpretaion of the "inherency" doctrine goes too far. Just like the applicant in both *Halleck* and *Caldwell,* Applicant here claims a novel purpose for a known substance: administering an effective amount of niacin to increase systemic tryptophan of dietarily replete humans. Mur. Decl., ¶6. Nothing in the prior art suggests as much. *Id.,* ¶¶ 7-8. The mere fact that others have observed that higher nutrient doses of niacin are sometimes taken by patients with HIV, and hypothesize that it may be "biologically plausible"[1] that high doses of niacin could slow the onset of AIDS does not render obvious Applicant's claim to a wholly different purpose. Applicant respectfully requests that the obvious rejection be withdrawn.

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[1] *See,* Tang et. al, at 948 (claiming theory is at best "biologically plausible").

6. Even if a § 103 rejection is proper, Examiner should reconsider the § 103 rejection because Applicant has provided evidence reflecting skepticism of experts, which rebuts an obviousness rejection.

"Expressions of disbelief by experts constitute strong evidence of nonobviousness." *Environmental Designs, Ltd. v. Union Oil of Cal.,* 713 F.2d 693 (Fed. Cir. 1983)(*citing United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1966)) (The patented process converted all the sulfur compounds in a certain effluent gas stream to hydrogen sulfide, and thereafter treated the resulting effluent for removal of hydrogen sulfide. Before learning of the patented process, chemical experts, aware of earlier failed efforts to reduce the sulfur content of effluent gas streams, were of the opinion that reducing sulfur compounds to hydrogen sulfide would not adequately solve the problem.); *see also,* MPEP§ 716.05

"The skepticism of an expert, expressed before these inventors proved him wrong, is entitled to fair evidentiary weight, . . . as are the five to six years of research that preceded the claimed invention." *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988); *Burlington Industries Inc. v. Quigg*, 822 F.2d 1581, 3 USPQ2d 1436 (Fed. Cir. 1987) (testimony that the invention met with initial incredulity and skepticism of experts was sufficient to rebut the prima facie case of obviousness based on the prior art).

In this case, prior to the filing of the patent application on June 30, 2000, experts in the field of infectious diseases scoffed at the notion that niacin might have some benefit in the treatment of retroviral infections. Mur. Decl., ¶ 13. In late 1998, experts in the field expressed skepticism:

> many HIV infected people take vitamin supplements and there have never been reports on any major effect on the clinical course except for vitamin A. Many individuals and researchers have ideas that vitamins may provide some clinical benefit in HIV infection but the niacin theory needs much better substantiation and of course some kind of clinical trial. Thus at this point the concept is so purely speculative...

See, Mur. Decl., ¶¶ 13-20 (emphasis supplied); *see also,* The Lancet peer review attached as Exhibit D to Mur. Decl..

Another expert was similarly skeptical. *See*, Mur. Decl., ¶ 18; *see also,* The Lancet peer review attached as Exhibit D to Mur. Decl.. The other expert also noted that while Tang, et al. claimed a positive clinical outcome with niacin, Tang's study may have been due to "confounding factors" and/or the presence of B vitamins. *Id.*

The USPTO was similarly skeptical the information relied on by Murray 1995. *See* Response, *supra*, Section 3, pages 24-25. Murray 1995 articles was based on *in vitro* data. *Id.* The USPTO was skeptical of the *in vivo* data, specifically:

> The specifications provide data only for inhibiting HIV in cells in culture. There is no data to substantial the alleged utility for treating human subjects infected with HIV. There is **no data to substantiate the alleged utility for treating human subjects infected with HIV**.... Without statistically significant data documenting the claimed method for treating patients, the person of ordinary skill in the art, knowing the unpredictability of extrapolating from in vitro results to in vivo performance, would have good reason to doubt the efficacy of applicant's invention.

See Mur. Decl., **Exhibit F**, USPTO office action, page 2-3, rejections under §101 and § 112 (emphasis supplied).

Murray's 1999 "niacin hypothesis" cited to Tang and Murray 1995 yet experts in the field scoffed at the "niacin hypothesis" -- very same papers cited by Examiner (Tang, Murray 1995) in support of the obvious rejection. As noted by the Federal Circuit, the skepticism of these experts prior to the filing of the application "constitute[s] strong evidence of nonobviousness." *Environmental Designs, Ltd. v. Union Oil of Cal.,* 713 F.2d 693 (Fed. Cir. 1983); (*citing United States v. Adams*, 383 U.S. 39 (1966)).

7. Even if a § 103 rejection is proper, Examiner should reconsider the § 103 rejection because Applicant has provided evidence reflecting long felt need for treating systemic tryptophan depletion in patients infected with a retrovirus.

Establishing a "long-felt need" for the invention rebuts a finding of obviousness. *See* MPEP § 716.04; § 2141. The infectious disease community has noted, evaluated and discussed that tryptophan depletion can be associated with patients infected with a retrovirus for at least the last sixteen years. Mur. Decl., ¶ 7. For example, attached to the Mur. Decl. as **Exhibit B** are eight articles that examine various aspects of plasma or serum tryptophan in HIV infected patients (referred to as the "eight articles"). Also included as part of **Exhibit B** is a summary that prepared by Dr. Murray. The eight articles are not exhaustive of all articles published, but examples of the types of articles that can be found in published medical literature.

The infectious disease community has been aware of the possibility of tryptophan depletion occurring in patients with HIV since at least as early as 1988. *See, e.g.,* Mur. Decl.; **Exhibit B.** The articles reflect the long-felt need for treating tryptophan depletion. *See id.* Nowhere, however, do the eight articles suggest the administration of niacin to restore tryptophan levels. *See id.* Similarly, applicant is aware of no articles that have ever suggested the administration of niacin to restore tryptophan levels. Thus, Applicant's invention is not obvious because it satisfies a long-felt need.

8. Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination an increase in systemic tryptophan necessarily flows from the teachings of Tang et. al and Murray et. al.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." MPEP § 2112, (Section

titled *Examiner Must Provide Rationale of Evidence Tending to Show Inherency)*(citing *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(empahsis in original). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency.]" *In Re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993)(quoting *In re Oelrich,* 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

In this case, the Examiner appears to claim that an increase in systemic tryptophan is an "inherent characteristic" that flows from teachings of Tang and Murray. An increase in systemic tryptophan, however, cannot be said to necessarily flow from the teachings of Tang and Murray. The teachings of Tang concede that the observational data they gathered did not necessarily support a conclusion that niacin has any effect at all:

> Since intakes of B-group vitamins are highly **intercorrelated**, further research is needed to determine if one or more of these nutrients is related to HIV-1 disease progression. Under these circumstances, **niacin may represent a marker** of overall intake of B-group vitamins rather that having any direct effect on immune function.

Tang et. al, at 948 (emphasis supplied). Tang, et. al concede that their findings have, at best, only "some biological plausibility." Tang et. al, at 948. More importantly, though, nothing in Tang et al suggests that niacin increases systemic tryptophan levels.

Similarly, an increase in systemic tryptophan cannot be said to necessarily flow from the *in vivo* teaching Murray et al. Murray et al evaluated nicotinamide as an inhibitor of HIV *in vitro*.

Finally, while there is a correlation between retroviral infection and tryptophan depletion there is significant interpatient variability. Mur. Decl., ¶ 6. Thus, not every patient infected with a retrovirus will necessarily require the intervention suggested by the invention disclosed in the application. *Id.* The invention disclosed in the application will specifically benefit patients in

need of therapy to maintain or increase their systemic tryptophan levels. *Id.*

If the Examiner does not withdraw the objection, Examiner must provide a basis in fact and/or technical reasoning to reasonably support that increased systemic tryptophan necessarily flows from the teachings of Tang et al and Murray et al as required by MPEP § 2112.

9. Applicant requests that the Examiner reconsider the obvious rejection because a *prima facie* case cannot be made when the prior art is unpredictable.

Pursuant to MPEP 706.02(j), an applicant is not required to submit evidence or a substantive response until a *prima facie* case is made. *In Re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993)("In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." (citations omitted)).

In this case, Applicant contends, and still contends, that the Examiner has not set forth a prima facie case of obviousness for the reasons described in Applicant's previous response dated January 16, 2002. "Obviousness cannot be predicated on what is unknown." *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, "a reasonable likelihood of success must [] be found in the prior art." MPEP 2142, *Establishing a Prima Facie Case of Obviousness*. According to the MPEP, "at least some degree of predictability is required." MPEP 2143.02. In this case, the prior art cited by the examiner provides no degree of predictability. Therefore, no *prima facie* case can be established.

On page 3 of the first Office Action dated 7/27/2001 (paper 4), Examiner stated that "[t]he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity." (emphasis supplied). Examiner continues to assert his unpredictability argument. (page 3 of paper 12). Applicant concedes that the "verbiage of page

3 (of paper 4) and the verbiage of page 3 (of paper 12) was used by the examiner to support a rejection under 35 U.S.C. § 112. However, the fact that the "verbiage" was used in a §112 rejection does mean it is irrelevant with respect to a *prima facie* analysis under § 103. The predictability (or unpredictability) of the relevant art must remain the same under §103 as it does under §112. The relevant art cannot be "unpredictable" when rejecting a claim under §112, while at the same time being predictable enough to establish a *prima facie* case of obviousness under § 103. Unpredictable under §112 means unpredictable under §103. The verbiage of page 3 (of paper 4 and 12) affirmatively states that the relevant art is "unpredictable"—at least with respect to a §112 rejection. Without predictability, the *prima facie* case of obviousness under § 103 fails. *See* MPEP 2143.02.

In addition, the prior art relied upon by the Examiner further reinforces the conclusion that the prior art is unpredictable. Not only did Tang et. al concede that the data they gathered does not necessarily support a conclusion that niacin had any effect at all on immune function, but Tang et. al admit that, as far as they can tell, niacin may be nothing more than a marker of B-group vitamins:

> Since intakes of B-group vitamins are highly **intercorrelated**, further research is needed to determine if one or more of these nutrients is related to HIV-1 disease progression. Under these circumstances, **niacin may represent a marker** of overall intake of B-group vitamins **rather that having any direct effect** on immune function.

(Tang et. al, at 948) (emphasis supplied).

In addition, the study conducted by Tang, et al was based on patient responses to questionnaires. Thus, the Tang study was observational not experimental. Tang, et al. expressly highlight several limitations to their study, including that the "food frequency questionnaire" has not been validated in any HIV-1 seropositive population (Tang et. al, at 950). More importantly,

though, Tang, et al. admit that dietary changes of the study's participants may not have any effect at all on disease progression. *Id.* In fact, dietary changes of the participants may be "a result of disease progression, rather than a cause." *Id.* At best, Tang, et. al merely claim that their "findings appear to have some biological plausibility." *Id.*

Similarly, the *in vivo* teaching of Murray et al. is similarly unpredictable. Murray et al expressly state that their extrapolation of *in vitro* data was merely speculation and hypothesis that could only be confirmed by *in vivo* data:

> **We speculate** that NAm works to inhibit one or more ADP-ribosylation steps which might otherwise deplete the infected cell of NAD.
>
> ...
>
> **If our original hypothesis** that HIV induces a pellagroid state **is correct**...
>
> ...
>
> **... if confirmed on an *in vivo* level.**

Murray et al, at 958-59 (emphasis supplied).

Thus, not only is the pharmaceutical art unpredictable as a whole, the prior art relied upon by the Examiner expressly concedes that their conclusions were speculation and hypothesis that needed further research and verification before they could be relied upon. Because the prior art fails the degree of predictability required by MPEP § 2143.02 and because—as the Examiner has pointed out—the relevant prior art is "unpredictable", the Examiner cannot establish a *prima facie* case of obviousness. As such, the obviousness rejection must be withdrawn.

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Conclusion

Applicant requests entry of claims 1,14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, and 33. Applicant now believes that the application is now in condition for allowance and kindly asks the Examiner for reconsideration thereof.

Respectfully submitted,

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